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Current issues in xenobiochemistry related to cumulative processes of chemical xenobiotics and pathobiochemistry - review

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Abstract

Xenobiochemistry, often considered as a subsequent domain of biochemistry, demanded attention due to its aspects of theoretic and applicative interest. Among them, the particularities of biochemical interactions and the extension towards biochemical pathology are distinguished. Its areas of interest include foods (with the risk of contamination), pharmaceutical products, and obviously products of strictly toxic interest (biocides).

An essential aspect in case of xenobiotics of food, pharmaceutical or strictly toxic interest is represented by their specificity to cumulate in the organisms. With reference to the cumulative features, it is mentioned that nowadays the levels of bioaccumulation, bioconcentration, biomagnification are being discussed more and more frequently, like in this work.

Obviously, the diversification of the chemical composition of xenobiotics, the expansion of technologies that can generate more xenobioderivatives, the difficulties sometimes introduced in verifying the traceability of raw materials (in food and pharmaceutical industry), gradually lead to the need of more in depth studies regarding pathobiochemistry with extension to pathophysiology.

Keywords: xenobiochemistry, cumulative processes, pathobiochemistry

Introduction

In scientific research in the field of life sciences it is important to make distinction between the metabolization of nutrients - as a field of biochemistry and the biotransformation of chemical xenobiotics - as a field of xenobiochemistry.

To this were added studies related to the dyshomeostasis of bioconstituents in tissues and biological fluids. Such investigations sought to elucidate the structure and amount of metabolites resulting from the metabolization of nutrients, respectively the structure and amount of primary xenobiotics and of residual xenobioderivatives formed during biotransformation.

Both processes can be at the origin of "molecular injuries" induced by atypical metabolic products, respectively by residual xenobioderivatives after biotransformation.

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In these conditions, the concept of "molecular pathology" - a name given in 1923 by Schade - gained a new meaning. It is mentioned that, over time, this concept has acquired a continuous extension. Currently - largo sensu - the concept of "biochemical pathology" is used [4, 19, 22, 23, 33].

Xenobiotics from the environment (water, air, soil), from processed foods and from drugs (mainly synthetic) systematically enter the human body. Thus, specific cumulative processes can gradually occur, which explains the fact that various chemical xenobiotics have been detected in biological fluids and tissues [5, 27]. In the case of cumulative processes specific to xenobiotics, their biological half-life in the living organism is also taken into account.

Chemical xenobiotics or the residual derivatives (xenobioderivatives) originating from biotransformation interact with metabolites. Afterwards, the resulting compounds are eliminated through the digestive, renal, respiratory and skin routes [12, 20, 31].

A special situation occurs in the case of perpetual exposure to the action of one/some xenobiotics, followed by retention and cumulative processes. Thus, a certain "persistence" is created (through repeated consumption) with inherent pathobiochemical and, further, pathophysiological risks.

1. Peculiarities of the domain of xenobiochemistry

Xenobiochemistry has the attributes of some subsequent fields of biochemistry. In xenobiochemistry there are studied certain substances (called xenobiotics) belonging to contaminating substances in food, pharmaceutical products, and even toxic substances, i.e. biocides.

In the case of chemical xenobiotics the concept of „biotransformation” is characteristic. The interactions occur in „specific biochemical pathways” [10, 18].

It is reminded that in the case of biochemistry, the defining concept is the „metabolism” which takes place on „natural biochemical pathways”.

In case of biotransformation the „specific pathways” are xenobiodegradattion and xenobiosynthesis. The characteristic interactions of these pathways occur simultaneously with the interactions of the natural biochemical pathways. Xenobiodgeradation can be followed by the formation of „residual xenobioderivatives”.

The presence in the organism of xenobiotics that enter by different ways as wll as of the residual xenobioderivatives represent a risk for triggering pathological processes at molecular level and known in pathobiohemistry as „biochemical injury” and afterwards at cellular level known as „cellular injury” and studied both in pathophysiology and morphopathology [15, 26, 34].

Obviously, in the pathological situations mentioned, there are preliminary stages in which cumulative processes can be distinguished.

2. Cumulative processes - characteristics

In assessing the presence and effects produced by chemical xenobiotics, there is still some confusion between the notions of bioconcentration, bioaccumulation and biomagnification. These notions, which characterize distinct cumulative processes, are not interchangeable [2, 29].

Cumulative processes - via food, drugs and water - depend on the composition of the substance, its physico-chemical properties, the conditions of exposure/administration, the duration of exposure, the concentration of the substance in the environment, etc.

Defining the notions of bioconcentration, bioaccumulation and biomagnification has distinct characterization criteria to consider. These include the "mode" of contamination occurence, the "specificity of retention" of a certain contaminant and the value of a "factor" that indicates the cumulative level - represented by the ratio between the concentration of the chemical compound in the contaminated organism and the concentration of the compound in the environment from which it was taken [8, 9, 10, 25].

For understanding the cumulative processes it is important to know the concepts of "trophic chain" and "trophic network". These concepts explain in a broader sense the fundamental problems of nutrition.

3. The concepts of "trophic chain" and "trophic network"

In the specialized literature, a distinction is made between the "trophic chain", i.e. nutritional chain and the "trophic network", i.e. trophic cycle [2, 8, 25].

The concept of "food chain" or "nutritional-chain" describes the transit of food (with the specific input of matter and energy) between a limited number of organisms in an ecosystem, i.e. autotrophs; heterotrophs (e.g. herbivores, carnivores).

The concept of "trophic cycle" (food-cycle) or "trophic network" (food-web) - represents a sum of trophic chains (biologically interconnected), present in an ecosystem. It actually defines all the food chains in an ecosystem. Historically, the concept of "food-cycle" was introduced in 1927 by Charles Elton (1900-1991) - an English zoologist considered one of the founders of ecology. Today it is usually called the "trophic network" and is understood as an interconnection of trophic chains.

The notions of bioconcentration and bioaccumulation in the case of food refer to the concept of "trophic chain", i.e. "food chain", characterizing certain organisms.

The notion of biomagnification refers to the concept of "trophic network", i.e. "food web".

Currently, in food science, a distinct field has been established from a theoretical and applied point of view, concerning "nutrivigilance". It can be defined as all the activities for the detection, evaluation, understanding and prevention of adverse effects related to the consumption of a food. It refers both to fresh foods (of vegetable, animal, mineral origin) and to prepared/processed foods intended for consumption. The data obtained are of interest to food safety and consumer protection.

More and more works have appeared in the field of nutrivigilance, and in some countries institutions have even been created with such declared objectives [21, 32].

In the case of drugs, the evaluation of cumulative processes specific to chemical xenobiotics is the object of interest of pharmacology (pharmacokinetics). In this framework there is also a special field of pharmacovigilance [7,24].

An overall view on trophicity brings back into attention the autotrophic and heterotrophic specificity in the nutrition of organisms. In this context, referring to the cumulative processes, it is reiterated that aquatic organisms take chemical substances from the hydrosphere, and terrestrial animals from the atmosphere and terrestrial environment [37].

4. Progressive accumulation of xenobiotics

4.1. Bioconcentration

The notion of bioconcentration defines a cumulative process and is mainly used to characterize the concentration of xenobiotics in aquatic organisms in relation to the concentration in water.

Bioconcentration - initially, in the acceptance of IUPAC (1993) - was defined as a process that leads to the increase of the concentration of a substance in an aquatic organism in relation to its concentration in the environment.

In physiology, bioconcentration is considered as a process by which a certain chemical compound (in this case a chemical xenobiotic in food) reaches higher concentrations in an organism compared to the concentration in the abiotic environment from which it was taken.

In the assessment of bioconcentration, a bioconcentration factor is used - noted as F_{bc} or B_{cf} (Bioconcentration Factor) represented by the ratio between the concentration of the substance (xenobiotic) in the organism (in tissues) - C_o and the concentration in the environment - C_{ma}.

The definition of a mathematical relationship for the bioconcentration factor (F_{bc}) can be rendered as follows:

$$F_{bc} = \frac{C_0}{C_{ma}}$$

This relationship was initially used in the field of hydrobiology to define the processes that characterize the concentration of chemicals in aquatic organisms.

For information, it is mentioned that in biochemistry and ecology the bioconcentration factor (F_{bc}) can be considered as a value parameter in evaluating the presence of a xenobiotic. So, in this regard, the use of the relationship has been extended.

4.2. Bioaccumulation

The uptake of chemical compounds (nutrients and xenobiotics) from food and water can lead - under certain conditions - to cumulative processes.

Numerous chemical xenobiotics reach higher concentrations in food under insanitation conditions, due to the (in excess) presence of some harmful organic and inorganic compounds in the environment.

The cumulative process has as consequence the increase of the concentration of xenobiotics in living organisms to higher amounts in relation to their concentration in the biotope (surrounding environment) in which they are located. In applications, the bioaccumulation factor – B_{af} can be determined. This is a ratio between the concentration of a xenobiotic in the organism (C_o) and its concentration in the environment, circumscribed to the ingested foods (C_a). The value may be expressed as:

$$F_{ba} = \frac{C_0}{C_a}$$

In nature, the bioaccumulation of a certain contaminant (xenobiotic) is achieved by the transfer of substances, via the "trophic chain".

4.3. Biomagnification

In physiology and pathophysiology biomagnification, also known as "bioamplification", may be defined by the increase in the concentration of a chemical substance (namely, a xenobiotic) following the transfer via the "*food web"*.

Biomagnification - a distinct form of cumulative processes - may be regarded as an evolutive sequence in an ecosystem in which the concentration of a certain chemical compound - xenobiotic (*e.g.* the pesticide DDT) reaches concentrations higher than those detected in the habitual environment. Applicative research conducts tests for determining the biomagnification factor - B_{mf}.

Regarding biomagnification, one may mention that, globally, it appears as a phenomenon of accumulative transfer of certain chemical xenobiotics inside a contaminated biocenosis.

Biomagnification - according to the Environment Protection Agency in the USA (2010) - is the result of a bio transfer process in which the concentration of the chemicals in the tissues of organisms on a superior trophic level exceeds the concentration of these substances in the tissues of organisms on an inferior trophic level.

The biomagnification potential is indicated by the increased quantum of chemical xenobiotics and of their biodegradation products (residual xenobioderivatives) in a certain organism reported to the consumed foods, as major sources.

In relation with biomagnification, the concept of "*secondary toxicity*" has been elaborated [8]. This concept makes reference to superior organisms (animals and humans), in whom the continuous accumulation of (chemical) xenobiotics occurs by the (long-term) ingestion of certain contaminated foods. Hence, the concept of secondary toxicity.

5. Pathogenesic effects of cumulative processes

Chemical xenobiotics present in food, in drugs and, generally, in the environment, may induce changes in the biochemical homeostasis followed by physiological/physiopathological disorders.

Gradually, occurs the so-called "chemical stress", caused by the increase in the concentration of xenobiotics and may cause physiopathological perturbations originating in the biochemical dyshomeostasis [3, 14].

Generally, the xenobiotics are considered "*chemical stressors"* present in the habitual environment. These may act upon the organisms affecting the physiological activities at lower levels of organisation (biomolecules, cells) advancing towards the upper levels (tissues, organs etc.) and, finally, towards organisms and populations [5, 8, 11].

Regarding xenobiotics and the post-cumulative effects, we must also discuss toxicity, as an expression of the pathobiochemical and physiopathological consequences they induce [16, 17, 35, 36]. It is mentioned under this aspect that scientific treaties in the field of food chemistry (published during the last decades), an increasing attention is paid to food toxicology [3, 6,13, 26, 30].

Also, data on legally enforced studies on the effects of food ingredients intoxication (additives, flavouring agents etc.), their testing methodologies etc. are also presented. Regarding the effects of chemical xenobiotics of food interest, certain conventional criteria have been accepted for the investigation of the toxigenic effect in:

- acute intoxication - by which the totality of toxic effects produced by the single dose which may cause death in 50% of the tested animals was established. The test lasts 24-48 hours, and the single dose used is called semilethal dose (DL_{50}).
- subacute intoxication - is revealed by the totality of toxic effects produced by the administration of a certain toxic compound in the same dose, in extended administration for

1/10 of the medium life expectancy of the respective species.

- chronic intoxication - represents the totality of toxic effects caused by the repeated administration of a toxic compound in equal doses throughout the entire life expectancy of the experimental animals. For this, experimental animals with a relatively short-medium life expectancy are used. In these, the teratogenic, mutagenic and carcinogenic effects are monitored.

Generally, when evaluating the effects of the passage of xenobiotics as such and/or of residual xenobioderivatives through the organism, attentive studies of the biotransformation phases completed by their biomonitoring are needed. Also, knowledge of the specific aspects of absorption, distribution (with possible retention or even accumulation) and elimination is of interest.

We are reiterating that in the case of biotransformation, the conversion takes place during the phases of xenobiodegradation and/or xenobiosynthesis. These phases - following various biotransformation pathways - generally result in the formation of high polarity compounds which have a lower toxicity and are more easily eliminated.

In the organism, most chemical xenobiotics are subjected to biotransformation. Exceptions are represented by the compounds with high polarity, *e.g.*: strong acids, strong bases, inorganic and organic compounds, as well as nonpolar compounds, *e.g.*: ethyl ether, veronal, toluene.

The status of xenobiotics distribution may be characterised by the evaluation and quantification of specific parameters in "xenobiokinetics*"*. For their denomination, we agree upon the use of the term "xenobiokinetic parameters".

Among the xenobiokinetic parameters, "clearance" and "half-life" are the most important. In xenobiochemistry, the status of the action of chemical stressors may be evaluated by the use of biomarkers.

Thus, at the cellular level, the following microscopic findings have been detected: alteration of intracellular membranes (endoplasmic reticulum, lysosomes in vegetal and animal cells and transport vesicles in vegetal cells); modification of micronuclei and others.

Also, at the molecular level, genotoxic effects may occur (e.g. formation of adducts with DNA); formation of nonspecific proteins (e.g. atypical metalloproteins, stress proteins, oncoproteins) etc.

At present, it is accepted that the gene changes in information macromolecules, especially in the nucleic acids of the genome, may have pathological consequences, determining severe biochemical injuries [1, 4, 7, 20, 28].

The problem of xenobiotics entered the attention of the European medical and veterinary organisms which created a Rapid Alert System for Food and Feed – RASFF legally based upon the EC Regulation 178/2002. Among the RASFF objectives, a priority is represented by the detection of residues of veterinary medicines and heavy metals in foods.

Conclusive data

Along with the industrial development (respectively of the processing methods), the increase of the environmental level of pollution with household, industrial, etc. residues, problems related to xenobiochemistry, starting from the presence of xenobiotics in food, pharmaceutical products and use of toxic substancs (biocides) show increased interest.

In the existing situation, issues related not only to „primary xenobiotics" that enter the body, but also to „residual xenobiotics" resulting from biotransformation processes (xenobiodegradation, respectively xenobiosynthesis) are deepened.

With the development of research in these fields, the studies on cumulative processes, i.e. bioconcentration, bioaccumulation, biomagnification in the organisms were extended.

As a consequence of the topics presented above, the idea to approach aspects related to cellular pathology is detached and was presented in a correlative framework in this paper.

Compliance with Ethics Requirements. Authors declare that they respect the journal's ethics requirements. Authors declare that they have no conflict of interest and all procedures involving human or animal subjects (if exist) respect the specific regulation and standards.

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